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Published in:
Cardiovascular Therapeutics

DOI:
[10.1111/1755-5922.12301](https://doi.org/10.1111/1755-5922.12301)

Publication date:
2017

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Kang, C-K., Pope, M., Lang, C., & Kalra, P. R. (2017). Iron Deficiency in Heart Failure: Efficacy and safety of intravenous iron therapy. *Cardiovascular Therapeutics*, 35(6), 1-8. [e12301]. <https://doi.org/10.1111/1755-5922.12301>

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Article type : Unsolicited Review

Iron Deficiency in Heart Failure: Efficacy and safety of intravenous iron therapy

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Keywords: Heart failure, Anaemia, Iron deficiency, Iron therapy

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This is the peer reviewed version of the following article: 'Iron Deficiency in Heart Failure: Efficacy and safety of intravenous iron therapy', *Cardiovascular Therapeutics*, which has been published in final form at <http://dx.doi.org/10.1111/1755-5922.12301>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

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Abstract

Aim:

To discuss the pathophysiology of iron metabolism in chronic heart failure (CHF), the current knowledge of the efficacy of intravenous (IV) iron therapy in patients with CHF and identify points of controversy as well as highlight areas for future research.

Discussion:

Iron deficiency is a recognised complication of many chronic conditions. Numerous studies have reported that iron deficiency is highly prevalent in patients with CHF and is associated with exercise intolerance, reduced quality of life, and increased risk of hospitalisation and mortality. Several small studies have demonstrated IV iron to be associated with improvements in symptoms, exercise capacity, quality of life, renal function, New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF), and reduction in NT-pro-brain natriuretic peptide (NT-proBNP) in patients with CHF and iron deficiency. Two larger scale trials confirming these results (FAIR-HF and CONFIRM-HF) have led to guideline recommendations that IV iron therapy should be considered in patients with CHF with reduced ejection fraction and iron deficiency (serum ferritin $<100\mu\text{g/L}$, or ferritin between $100\text{--}299\mu\text{g/L}$ and transferrin saturation $<20\%$) in order to provide symptomatic relief and improve exercise capacity and quality of life.

Conclusion:

IV iron therapy improves symptoms, exercise capacity, and quality of life, at least in the short to intermediate time. However, there is still currently no standardised criteria used to define iron deficiency and the underlying mechanism of iron deficiency in CHF remains incompletely

understood. Further work is required to improve the ability to identify iron deficiency in patients with CHF and evaluate the effect of iron repletion on hard end-points including hospitalisation and mortality.

Introduction

Worldwide approximately one-third of the general population is affected by iron deficiency, making it the most common nutritional disorder.^[1-3] Iron deficiency is a recognised complication of chronic conditions such as inflammatory bowel, rheumatoid, and chronic kidney disease.^[4-6] As an essential micronutrient, iron has a central role in many metabolic processes. Due to its ability to switch between two oxidative states, ferrous (Fe^{2+}) and ferric (Fe^{3+}), iron is an efficient cofactor for several enzymes which help catalyse numerous biochemical reactions.^[7-8] Iron is a component of haemoglobin, which is crucial for oxygen transport to tissues. It also plays a role in oxygen storage (myoglobin), oxidative metabolism (component of oxidative enzymes and respiratory chain proteins), and is involved in the synthesis and breakdown of carbohydrates, lipids, and nucleic acids.^[7-10]

It is increasingly recognised that many patients with chronic heart failure (CHF) have associated iron deficiency. These patients experience worse symptoms compared to those who are iron replete and are at a higher risk of morbidity and mortality. This article discusses the prevalence of iron deficiency in heart failure, its underlying pathophysiology, and examines current clinical practice in the management of iron-deficient CHF patients. This article also identifies points of controversy and highlights areas for future research.

Iron metabolism and aetiology of iron deficiency in chronic heart failure

Although iron plays an important physiological role, an excess leads to significant toxicity and end-organ damage as seen in disease states of iron overload and inherited defects in iron metabolism such as hereditary haemochromatosis. As there is no specific mechanism for iron excretion, iron absorption and subsequent metabolism is tightly regulated. Homeostasis is then maintained by loss of iron through the turnover of skin and gut epithelial cells and bleeding.^[11]

Iron is primarily absorbed in the duodenum and jejunum via the divalent metal transporter protein on the luminal cell membrane. Ferric iron is reduced to its ferrous form by the enzyme ferric reductase and cytoplasmic ferrous iron is either packaged as ferritin for intracellular storage or transported across the basolateral membrane into the circulation. This process involves oxidation back to its ferric form by the enzyme hephaestin oxidase and export through ferroportin iron channels allowing absorbed iron to be transported through the circulation bound to transferrin.^[11]

Circulating iron is avidly taken up by hepatocytes, splenic cells, and bone marrow. Iron is incorporated into haem for bone marrow haematopoiesis or packaged as ferritin for iron storage particularly within the liver and spleen. Senescent erythrocytes are broken down by reticuloendothelial macrophages in the liver and spleen releasing further iron for either storage or circulation.^[11-12]

Distinguishing between stored and circulating iron is key to characterising iron deficiency, which can be classified as either absolute or functional.^[12-13] Absolute deficiency represents a depletion of iron stores whilst functional deficiency includes:

1. Normal iron stores but impaired mobilisation of iron into the circulation thereby restricting iron availability for cell metabolism and erythropoiesis.

2. An insufficient supply of iron to meet the demands of enhanced erythropoiesis brought about by either anaemia of another cause or excessive endogenous erythropoietin production.

Although ferritin is the predominant form of intracellular stored iron, a proportion of this enters the circulation. Serum ferritin levels can therefore serve as a surrogate marker of iron stores. Systemic inflammation however, results in the release of acute phase reactants, including ferritin, therefore limiting the validity of the relationship between serum ferritin levels and levels of stored iron in many chronic conditions. Perhaps more important is the amount of circulating iron available for cell metabolism. This can be estimated as a percentage of circulating transferrin saturated with iron (T_{SAT}).^[13]

Many pro-inflammatory cytokines have been implicated in the progression of CHF. Of these, the most important ones appear to be tumour necrosis factor α (TNF α), interleukin (IL) 1, and IL-6.^[14] In mice models, both TNF α and IL-1 induce the synthesis of ferritin by macrophages and hepatocytes.^[15-16] Divalent metal transporter 1 (DMT1), a transmembrane iron transport protein, is involved in the uptake of iron by macrophages and is up-regulated in the presence of TNF α , interferon- γ , and lipopolysaccharide.^[17-18] These pro-inflammatory cytokines also stimulate retention of iron in macrophages by down-regulating the expression of ferroportin.^[18] Ferroportin is therefore involved in the release of iron from macrophages as well as the transfer of absorbed iron to the systemic circulation.^[19] The discovery of hepcidin, an acute-phase protein, furthered the understanding of the relationship between the inflammatory immune response and iron homeostasis. Both IL-6 and lipopolysaccharide induce hepcidin expression and production in the liver. Results from mice models suggest that hepcidin may be centrally involved in the diversion of iron traffic by reducing duodenal iron absorption across the basolateral enterocyte membrane and blocking iron release from macrophages.^[20] Consequently there is limited iron available for

utilisation by erythroid progenitor cells, thus resulting in iron-restricted erythropoiesis as well as adversely impacting on the other key physiological roles of iron.

However, iron metabolism has yet to be fully investigated in patients with CHF and it remains unknown to what extent data from animal models can be extrapolated and applied to the clinical setting. It is tempting to link iron deficiency in CHF with associated inflammation and to suggest that hepcidin may have a central role in the inhibition of iron absorption.^[21] Recent studies, however, found rather low circulating levels of hepcidin in patients with CHF and reported no association between levels of pro-inflammatory cytokines (such as IL-6) and overexpression of hepcidin.^[22-24] Although markers of inflammation increased with worsening functional class, the inverse was true for hepcidin despite iron deficiency and iron-restricted erythropoiesis becoming increasingly common. Importantly, circulating levels of erythropoietin are often raised in heart failure, being higher in patients with worse functional class and are correlated with adverse prognosis.^[12] Erythropoietin is a powerful suppressor of hepcidin production and this may to some extent explain the lower levels observed in those with worse symptoms. The underlying mechanism of iron deficiency in CHF remains incompletely understood and further work is needed to fully elucidate the precise pathophysiology, and this in turn may influence treatment strategies.

Diagnosing iron deficiency

As outlined above, iron exists in stored intracellular, circulating, and utilised forms; the latter predominantly within erythrocyte haemoglobin. Levels of all forms vary considerably and movement between them involves complex regulation in response to changing metabolic requirements and various pathophysiological processes. An optimal diagnostic test would simply and accurately measure all forms of iron as well as total body iron levels. Unfortunately, no such test exists. Table 1 summarises the various blood tests used to diagnose iron deficiency.

Bone marrow biopsy is considered the 'gold standard' for evaluating iron status. This has the advantage of directly measuring iron stored within bone marrow and available for haematopoiesis. However, it is an invasive, uncomfortable and relatively complicated test to perform therefore significantly limiting its clinical applicability. In the absence of a single diagnostic test we rely on a combination of serum biomarkers. The most widely used of these is ferritin. Intracellular iron is stored as a protein bound complex known as ferritin. Although intracellular levels cannot be measured, a proportion crosses the cell membrane and enters the circulation. Quantification of circulating levels serve as a surrogate measure of iron stores. A low ferritin indicates iron deficiency. Ferritin however is also an acute phase protein released from the liver in response to inflammation thereby significantly reducing its diagnostic accuracy – in particular a 'normal' ferritin does not exclude iron deficiency in the context of co-existing inflammatory immune activation. Circulating iron is also measurable. However, this has a number of limitations. Serum iron levels vary considerably depending on intake and physiological requirements and may be maintained even as iron stores become significantly depleted. Circulating iron is found predominantly bound to its specific carrier protein, transferrin. Levels of circulating iron are therefore strongly influenced by levels of serum transferrin. Furthermore, transferrin is produced in response to low iron stores and increasing demands. Measurements of either serum iron or circulating transferrin alone therefore poorly reflect iron levels. The percentage of transferrin saturated with iron can also be measured. In iron deficiency, iron levels fall whilst transferrin increases resulting in fewer binding sites occupied and lower percentage transferrin saturation.

The major studies of iron deficiency in heart failure adopt a definition combining ferritin and transferrin saturations. Although in physiological circumstances, a ferritin above 30ng/L is considered normal, in an inflammatory state this cut off results in poor sensitivity. Instead, a ferritin of <100ng/L or a value of between 100 and 300ng/L with transferrin saturations <20% have been deemed to suggest iron deficiency.

Prevalence and prognosis of iron deficiency in heart failure

In recent years, there has been increased focus on the clinical importance of iron deficiency in patients with CHF. It is a frequent co-morbidity with varying prevalence depending on study criteria and the definition of iron deficiency used. For example, in one study of 1506 stable CHF patients with both preserved and reduced left ventricular systolic function, 50% were reported to be iron deficient.^[25] When analysed according to haemoglobin level, 46% of those without anaemia and 61% of those with anaemia were iron deficient.^[25] These results are similar to a recently published study of 4456 patients referred to a single outpatient heart failure service, which identified iron deficiency in 43-68% of patients with anaemia and 14-35% of those with a normal haemoglobin depending on the definition of iron deficiency used.^[26] There has only been one published study using the gold standard technique of bone marrow analysis, which examined 37 anaemic patients with advanced severe heart failure and demonstrated iron deficiency in 73%.^[27]

Many studies have shown that iron deficiency is associated with exercise intolerance, reduced quality of life, and increased risk of hospitalisation and mortality in CHF patients.^[28-30] Although iron deficiency is frequently related to anaemia, it is an independent predictor of symptom severity, exercise tolerance, and quality of life irrespective of haemoglobin status.^[25,29-30] One study analysed 3 years of follow-up of 546 patients with CHF secondary to left ventricular systolic dysfunction (LVEF \leq 45%) attending outpatient clinics or admitted to a tertiary referral cardiology centre.^[29] Event-free survival (event defined as all-cause death and transplantation) was 54% in those with iron deficiency versus 67% in those without (Figure 1).^[29] Analysis of a cohort of patients with both preserved and reduced left ventricular systolic function demonstrated an association between both anaemia and iron deficiency with higher New York Heart Association (NYHA) functional class. As seen in Figure 2, iron deficiency was associated with increased mortality, with an even stronger relationship when associated with anaemia.^[25]

Therapeutic interventions:

Prior to considering specific treatment of iron deficiency, it is worth discussing the role of erythropoiesis stimulating agents (ESA) in patients with CHF. Recognising the association of anaemia with adverse outcomes in CHF, several small studies evaluated the potential benefit of ESA with encouraging results that suggested improvement in symptoms and reduction in hospital admissions.^[31-35] These led to the RED-HF trial,^[36] a randomised, double-blind study designed to ascertain whether treatment with the ESA darbepoietin alfa improves clinical outcomes in CHF patients with anaemia. This double blind study of 2278 patients with CHF (LVEF \leq 40%) and mild-to-moderate anaemia (defined as haemoglobin between 9.0 and 12.0g/dL) were recruited and assigned to receive either darbepoietin alfa or placebo. Participants in the active treatment arm were given the drug to achieve a haemoglobin target of 13.0g/dL. The primary endpoint was a composite of death from any cause or first hospitalisation for worsening heart failure. The primary endpoint occurred in 576 patients (50.7%) of 1136 patients in the active treatment arm and in 565 (49.5%) in the placebo group (P=0.87). A total of 42 patients (3.7%) in the darbepoietin alfa group experienced a fatal or non-fatal stroke as opposed to 31 patients (2.7%) in the placebo group (P=0.23). Reports of thromboembolic adverse events were received from 153 patients (13.5%) and 114 patients (10.0%) from the darbepoietin alfa group and placebo group, respectively (P=0.01). Darbepoietin alfa therefore did not reduce the rate of mortality or hospitalisation among patients with CHF and associated anaemia but conferred a significant increase in the risk of thromboembolic events. This study served to eliminate erythropoietin as a standard treatment for anaemia in patients with CHF.

Iron replacement

Several small studies reported that intravenous (IV) iron was associated with improvements in symptoms, exercise capacity, quality of life, renal function, NYHA functional class and LVEF, and reduction in NT-proBNP in CHF patients with iron deficiency anaemia.^[37-39] Further data supporting benefit on exercise capacity have come from a recent study which demonstrated a significant

improvement in peak oxygen uptake (VO_2) among symptomatic patients with stable heart failure treated with IV iron for 24 weeks as compared with placebo ($P=0.02$).^[40] In contrast, oral iron appears to have little effect on oxygen consumption or iron stores in patients with CHF.^[41] This is likely due to the impaired duodenal absorption of iron in the context of the chronic inflammatory state described above.

To date, there have been two larger-scale clinical trials which reported the beneficial effects of IV iron therapy in CHF patients with iron deficiency.^[21,42] The FAIR-HF trial^[42] was a randomised, double-blind study designed to determine whether the administration of IV iron (ferric carboxymaltose) conferred symptomatic benefit in iron-deficient CHF patients, either with or without anaemia. In this study, 459 patients with CHF and NYHA functional class II or III were enrolled. Cut-off points for LVEF were $\leq 40\%$ and $\leq 45\%$ for NYHA class II and III respectively. Iron deficiency was defined as ferritin $< 100\mu\text{g/L}$, or between 100 and $299\mu\text{g/L}$ with transferrin saturation $< 20\%$. The subjects were randomly assigned to receive either IV ferric carboxymaltose or saline (placebo). The primary endpoints were the self-reported Patient Global Assessment and NYHA functional class, both recorded at week 24. Among the patients who were given ferric carboxymaltose, 50% reported being much or moderately improved, and 47% were in NYHA functional class I or II. In comparison, 28% of patients in the placebo arm reported being much or moderately improved, and 30% were in NYHA functional class I or II ($P<0.001$). No significant differences were found between anaemic and non-anaemic patients (anaemia defined as haemoglobin $< 12.0\text{g/dL}$ for both men and women). The second study, known as CONFIRM-HF trial,^[21] was a multi-centre, double-blind, placebo-controlled trial designed to evaluate the effects and safety (to one year) of IV iron therapy in iron-deficient CHF patients. A total of 304 CHF patients with LVEF $\leq 45\%$ were recruited with the same definitions of iron deficiency as in FAIR-HF. Patients were randomised in a 1 : 1 ratio to receive either IV ferric carboxymaltose or saline (placebo) for 52 weeks. The primary endpoint was the change in 6-minute-walk-test (6MWT) distance from baseline

to week 24. IV ferric carboxymaltose was associated with significantly greater improvement in 6MWT distance at week 24 of $33 \pm 11\text{m}$ over the placebo group ($P=0.002$). The beneficial effects of iron therapy were sustained throughout the period of study. Furthermore, although it was not powered to evaluate this, IV iron was associated with a reduction in the risk of hospitalisation for worsening heart failure (HR 0.39, 95% CI 0.19-0.82, $P = 0.009$).

A recent meta-analysis by Jankowska et al.^[43] examined evidence from five randomised controlled trials,^[21, 39, 42, 44-45] involving a total of 851 patients – the majority being from FAIR-HF and CONFIRM-HF. IV iron therapy improved symptoms, exercise capacity, quality of life, and clinical outcomes, regardless of concomitant anaemia. Interestingly, the risk of cardiovascular hospitalisation, heart failure hospitalisation, cardiovascular death, and all-cause death appeared to be significantly reduced by IV iron therapy. Table 2 summarises the key results from the meta-analysis.

Current guidelines

In the latest clinical guideline published by the Scottish Intercollegiate Guidelines Network (SIGN) on management of CHF,^[46] patients with reduced ejection fraction, NYHA class III with an LVEF $\leq 45\%$, or NYHA class II, LVEF $\leq 40\%$, with a haemoglobin level of 9.5 to 13.5g/dL and iron deficiency (defined as ferritin $< 100\mu\text{g/L}$, or transferrin saturation $< 20\%$ with ferritin 100-300 $\mu\text{g/L}$) should be *considered* for IV iron therapy. IV ferric carboxymaltose is also shown to be cost-effective (£12,482 per QALY gained).^[47] In addition, the SIGN guidelines state that erythropoietin is not recommended for CHF patients with reduced ejection fraction and anaemia, mainly due to the absence of beneficial effects and the increased risk of thromboembolic adverse events.^[46]

The European Society of Cardiology (ESC) has also recently recommended that IV iron be considered in symptomatic patients with heart failure with reduced ejection fraction and iron deficiency (same definitions applied as the SIGN guidelines) – Class IIa recommendation and Level A evidence. The primary purpose of this recommendation is for symptom alleviation and to improve exercise capacity and quality of life.^[48]

The latest update published by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (ACC/AHA/HFSA) recommended that IV iron *may be considered* in patients with NYHA class II and III and iron deficiency (ferritin < 100ng/mL or 100-300ng/mL if transferrin saturation < 20%) to improve functional status and quality of life (Class IIb recommendation and Level B-R evidence).^[49] However, the report also stated that a strong recommendation for IV iron replacement can only be made once results from a well-designed trial evaluating its effects on morbidity and mortality are available.

Future challenges

Major gaps of knowledge still exist. Although serum ferritin has been used in several of the studies, increasing amounts of data suggest that serum ferritin is not a robust indicator of iron deficiency.^[26] Patients with CHF are less likely to have a low serum ferritin compared to patients without CHF. This may be attributed to the fact that ferritin is an acute-phase reactant which may be elevated in response to the underlying inflammatory process in CHF.^[14-20] Consequently, iron deficiency may be missed if based on serum ferritin concentration as high levels of serum ferritin may reflect inflammation rather than iron repletion. Many patients with serum ferritin < 100µg/L were also found not to have anaemia, thus suggesting a poor correlation between serum ferritin levels and prevalence of anaemia.^[26] Therefore, the validity of serum ferritin as a tool used to define iron deficiency is questionable and further work is needed to evaluate other haematinic factors which may potentially be a better indicator of iron deficiency.

In addition, the longer-term impact of iron repletion on CHF hospitalisation, overall hospitalisation (used as an index of both morbidity and cost-effectiveness), cardiovascular mortality, and safety is still poorly understood.^[50] An ongoing UK based study, IRONMAN,^[50] is a prospective, randomised open-label, blinded endpoint trial aiming to evaluate these issues. The primary objective is to compare the additional effect of an IV iron regimen (iron isomaltoside-1000) when added to standard guideline-indicated therapy on cardiovascular mortality and recurrent hospitalisations due to heart failure in patients with CHF secondary to left ventricular systolic dysfunction and iron deficiency. A total of 1300 patients will be recruited with the study period planned to last for approximately 4.5 years. Further outcome studies are planned in Germany and the United States.

Conclusion

Iron deficiency is very common in CHF and associated with an increased morbidity and mortality. IV iron therapy improves symptoms, exercise capacity, and quality of life, at least in the short to intermediate time. However, there is still currently no standardised criteria used to define iron deficiency and the underlying mechanism of iron deficiency in CHF remains incompletely understood. Further work is required to improve the ability to identify iron deficiency in patients with CHF and evaluate the effect of iron repletion on hard end-points including hospitalisation and mortality.

Declaration of conflicting interest

Both CK and MP declare no conflict of interest. CCL reports having received speaker fees/advisory boards from Novartis, MSD, Astra Zeneca, and Servier. PRK reports having received research grants from Alere, Medtronic, Pharmacosmos, and Servier. PRK also reports having received speaker fees/advisory boards from Alere, Amgen, BMS, Janssen, Novartis, Pfizer, Pharmacosmos, Servier, and Vifor.

References

1. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; 370(9586): 511-520.
2. Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999; 341(26): 1986-1995.
3. Clark SF. Iron deficiency anemia: diagnosis and management. *Curr Opin Gastroenterol* 2009; 25(2): 122-128.
4. Gomollon F, Gisbert JP. Anemia and inflammatory bowel diseases. *World J Gastroenterol* 2009; 15(37): 4659-4665.
5. Baker JF, Ghio AJ. Iron homeostasis in rheumatic disease. *Rheumatology (Oxford)* 2009; 48(11): 1339-1344.
6. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352(10): 1011-1023.
7. Anderson GJ, Vulpe CD. Mammalian iron transport. *Cell Mol Life Sci* 2009; 66(20): 3241-3261.
8. Cairo G, Bernuzzi F, Recalcati S. A precious metal: Iron, an essential nutrient for all cells. *Genes Nutr* 2006; 1(1): 25-39.
9. Fairbanks V, Beutler E. Iron deficiency. In: Beutler E, ed., *Williams Hematology*. 6th ed. New York: McGraw-Hill; 2001. p295-304 and 447-450.
10. Dunn LL, Suryo Rahmanto Y, Richardson DR. Iron uptake and metabolism in the new millennium. *Trends Cell Biol* 2007; 17(2): 93-100.
11. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013; 34(11): 816-829.
12. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardiol* 2011; 8(9): 485-493.

13. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010; 116(23): 4754-4761.
14. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart* 2004; 90(4): 464-470.
15. Alvarez-Hernandez X, Liceaga J, McKay IC, Brock JH. Induction of hypoferremia and modulation of macrophage iron metabolism by tumor necrosis factor. *Lab Invest* 1989; 61(3): 319-322.
16. Torti FM, Torti SV. Regulation of ferritin genes and protein. *Blood* 2002; 99(10): 3505-3516.
17. Andrews NC. The iron transporter DMT1. *Int J Biochem Cell Biol* 1999; 31(10): 991-994.
18. Ludwiczek S, Aigner E, Theurl I, Weiss G. Cytokine-mediated regulation of iron transport in human monocytic cells. *Blood* 2003; 101(10): 4148-4154.
19. Pietrangelo A. Physiology of iron transport and the hemochromatosis gene. *Am J Physiol Gastrointest Liver Physiol* 2002; 282(3): G403-G414.
20. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 2004; 113(9): 1271-1276.
21. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015; 36(11): 657-668.
22. Jankowska EA, Kasztura M, Sokolski M, Bronisz M, Nawrocka S, Oleskowska-Florek W, Zymliński R, Biegus J, Siwolowski P, Banasiak W, Anker SD, Filippatos G, Cleland JG, Ponikowski P. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements

identifies patients at the highest risk of death after an episode of acute heart failure. *Eur Heart J* 2014; 35(36): 2468-2476.

23. van der Putten K, Jie KE, van den Broek D, Kraaijenhagen RJ, Laarakkers C, Swinkels DW, Braam B, Gaillard CA. Hepcidin-25 is a marker of the response rather than resistance to exogenous erythropoietin in chronic kidney disease/chronic heart failure patients. *Eur J Heart Fail* 2010; 12(9): 943-950.

24. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, Macdougall IC, Weiss G, McMurray JJ, Anker SD, Gheorghiade M, Ponikowski P. Iron status in patients with chronic heart failure. *Eur Heart J* 2013; 34(11): 827-834.

25. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013; 165(4): 575-582.e3.

26. Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, Wong K, Rigby A, Goode K, Clark AL. Prevalence and outcomes of anemia and haematinic deficiencies in patients with chronic heart failure. *JAMA Cardiol* 2016; 1(5): 539-547.

27. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, Tsagalou EP, Maroulidis GD, Alexopoulos GP, Kanakakis JE, Anastasiou-Nana MI. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol* 2006; 48(12): 2485-2489.

28. Okonko DO, Mandal AK, Missouri CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011; 58(12): 1241-1251.

29. Jankowska EA, Rosentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron

deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010; 31(15): 1872-1880.

30. Comin-Colet J, Enjuanes C, Gonzalez G, Torrens A, Cladellas M, Merono O, Ribas N, Ruiz S, Gomez M, Verdu JM, Bruguera J. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. *Eur J Heart Fail* 2013; 15(10): 1164-1172.

31. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; 35(7): 1737-1744.

32. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001; 37(7): 1775-1780.

33. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003; 107(2): 294-299.

34. van der Meer P, Groenveld HF, Januzzi JL Jr, van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. *Heart* 2009; 95(16): 1309-1314.

35. Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2007; 49(7): 753-762.

36. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen DJ, RED-HF Committees, RED-HF Investigators. Treatment of anemia with darbepoietin alfa in systolic heart failure. *N Engl J Med* 2013; 368(13): 1210-1219.
37. Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, Chapman CM. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol* 2006; 48(6): 1225-1227.
38. Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007; 50(17): 1657-1665.
39. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008; 51(2): 103-112.
40. van Veldhuisen DJ, Ponikowski P, Metra M, et al. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure (EFFECT-HF): A Randomized, Controlled Study. AHA 2016 (abstract).
41. Lewis GD, Semigran MJ, Givertz MM, Malhotra R, Anstrom KJ, Hernandez AF, Shah MR, Braunwald E. Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction: Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure. *Circ Heart Fail* 2016; 9(5) pii: e000345.
42. Anker SD, Comin-Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan B, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA,

Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361(25): 2436-2448.

43. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016; 18(7): 786-795.

44. Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007; 50(17): 1657-1665.

45. Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol* 2013; 168(4): 3439-3442.

46. SIGN 147. *Management of chronic heart failure*. March 2016. [Online] Available from: <http://www.sign.ac.uk/guidelines/fulltext/147/index.html> [Accessed 7th March 2017].

47. Gutzwiller FS, Schwenkglenks M, Blank PR, Braunhofer PG, Mori C, Szucs TD, Ponikowski P, Anker SD. Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. *Eur J Heart Fail* 2012; 14(7): 782-790.

48. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of

Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37(27): 2129-2200.

49. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update to the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; 70(6): 776-803.
50. Effectiveness of Intravenous Iron Treatment vs Standard Care in Patients With Heart Failure and Iron Deficiency: a Randomised, Open-label Multicentre Trial (IRONMAN). [Online] Available from: <https://clinicaltrials.gov/ct2/show/NCT02642562> [Accessed 7th March 2017].

Table 1: Summary of blood tests used to diagnose iron deficiency

Test	Strengths	Limitations
Ferritin	1. Measures stored iron 2. Not affected by short term variations in iron intake	1. Affected by inflammatory states limiting sensitivity 2. Affected by liver disease
Serum iron	1. Direct measurement	1. Does not reflect iron stores 2. Highly variable with intake and metabolic requirements
Serum transferrin	1. Reflects varying metabolic requirements 2. Not affected by inflammatory states	1. Falsely low in liver disease 2. Not a direct measurement of iron levels
Transferrin saturations	1. Not affected by inflammatory states 2. Measures transported iron available for cell uptake	1. Does not directly measure iron stores

Table 2. Summary of results of the meta-analysis of iron therapy in heart failure by Jankowska et al.^[43]. (EQ-5D – European Quality of Life, HF – Heart failure, KCCQ – Kansas City Cardiomyopathy

Questionnaire, LVEF – Left Ventricular Ejection Fraction, MLHFQ – Minnesota Living with Heart

Failure Questionnaire, 6MWT – 6 Minute Walking Test, N/A - Not applicable, PGA – Patient Global

Assessment)

	Tobili^[44]	FERRIC-HF^[39]	FAIR-HF^[42]	IRON-HF^[45]	CONFIRM-HF^[21]	Meta-analysis^[43]
Number randomised (n=)	40	35	459	16	301	851
Follow up period	5 months after treatment	2 weeks after treatment	24-26 weeks	3 months	52 weeks	-
Outcome	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
All cause death	N/A	1.47 (0.06; 38.91)	0.62 (0.17;2.36)	1.25 (0.09;17.65)	0.85 (0.38;1.91)	0.83 (0.43;1.59) p=0.5671
Cardiovascular death	N/A	1.47 (0.06; 38.91)	0.50 (0.12; 2.02)	N/A	0.92 (0.39; 2.15)	0.80 (0.39; 1.63) p=0.5405
All-cause death or cardiovascular hospitalisation	N/A	0.24 (0.03; 1.73)	0.44 (0.24; 0.84)	N/A	0.45 (0.28; 0.73)	0.44 (0.30; 0.54) p<0.0001
Cardiovascular death or hospitalisation for worsening heart failure	N/A	N/A	0.41 (0.18; 0.93)	N/A	0.38 (0.21; 0.68)	0.39 (0.24; 0.63) p=0.0001
HF hospitalisation	0.07 (0.000; 1.34)	0.20 (0.02; 2.43)	0.38 (0.14; 1.04)	N/A	0.27 (0.13; 0.56)	0.28 (0.16; 0.50) p<0.0001
	Mean difference between groups	Mean difference between groups	Mean difference between groups	Mean difference between groups	Mean difference between groups (95%	Mean difference between groups

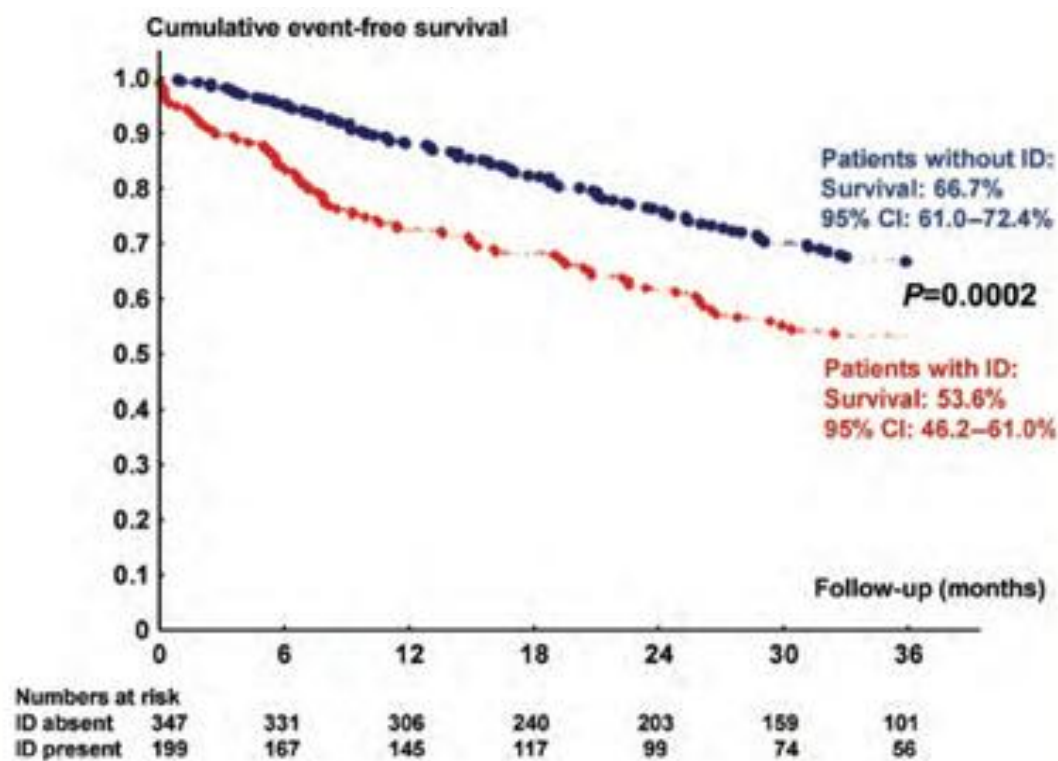
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	CI)	(95% CI)
6MWT distance	N/A	N/A	28.4 (13.95; 42.85)	N/A	38.40 (12.80; 64.00)	30.82 (18.23; 43.40) p<0.0001
NYHA class	-1.30 (-1.77; -0.83)	-0.60 (-0.96; -0.24)	-0.25 (-0.37; -0.13)	N/A	-0.28 (-0.49; -0.06)	-0.54 (-0.87; -0.21) p=0.0013
LVEF	-6.4 (-9.32; -3.48)	1.0 (-2.80; 4.80)	N/A	N/A	N/A	-2.8 (-10.05; 4.45) p=0.4485
EQ-5D score	N/A	N/A	5.70 (2.04; 9.36)	N/A	2.4 (-1.34; 6.14)	4.07 90.84; 7.310 p=0.0136
KCCQ score	N/A	N/A	6.60 (2.72; 10.48)	N/A	4.40 (0.45; 8.35)	5.52 (2.75; 8.29) p,0.0001
PGA	N/A	1.70 (0.58; 2.82)	0.63 (0.35; 0.91)	N/A	0.52 (0.06; 0.98)	0.70 (0.31; 1.09) p=0004
MLHFQ score	-20.00 (-24.04; -15.96)	13.00 (-27.17; 1.17)	N/A	N/A	N/A	-19.47 (-23.36; -15.59) p<0.0001

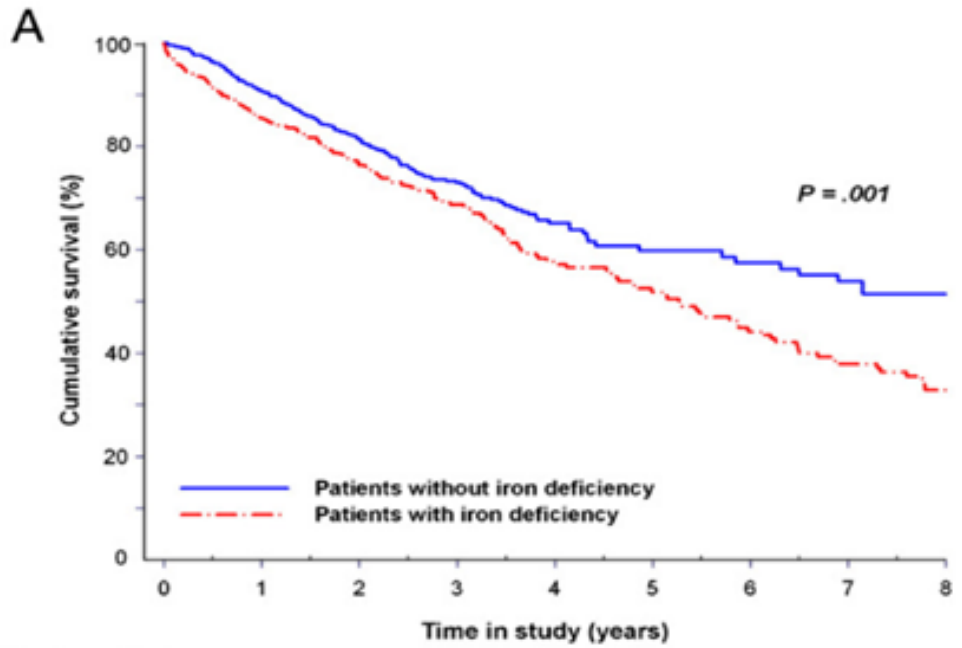
Figure Legends

Figure 1. 3-year event free survival (all-cause death and transplantation) in 546 patients with chronic heart failure secondary to left ventricular systolic dysfunction with versus without iron deficiency.

(From Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J. 2010; 31(15): 1872-80; Used with permission)

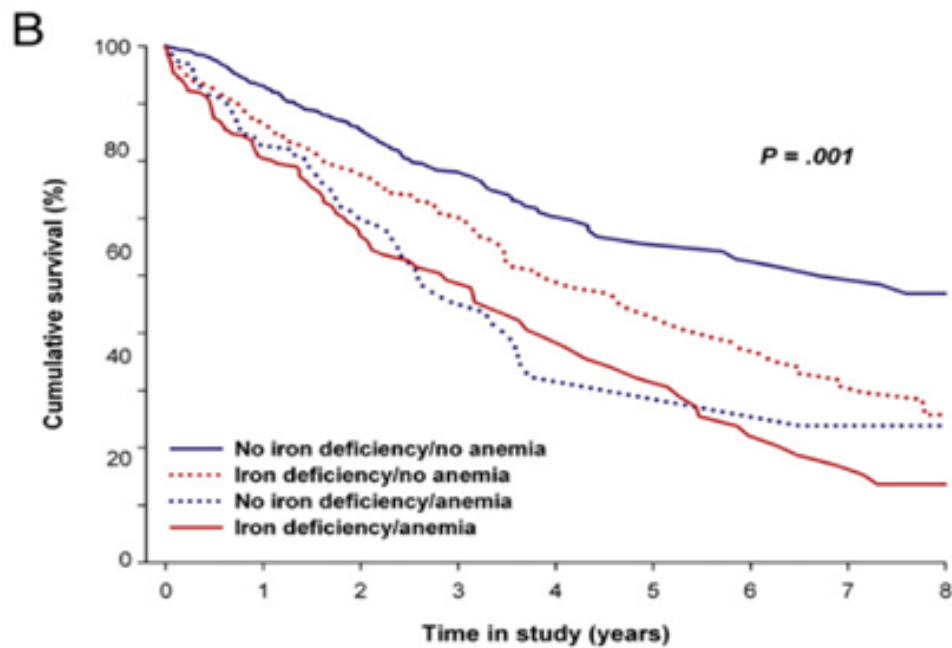
Figure 2 A. The presence of iron deficiency is associated with reduced survival in chronic heart failure patients with both preserved and impaired left ventricular systolic function. **B.** Iron deficiency and anaemia are cumulatively associated with reduce survival with the effect of iron deficiency appearing to have greater significance to anaemia alone. (From Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J.* 2013; 165(4): 575-82.e3.; Used with permission)





Numbers at risk:

ID absent	753	386	104	63	40
ID present	753	343	100	49	33



Numbers at risk:

No ID/no anemia	589	328	86	38	31
ID/no anemia	492	256	76	50	26
No ID/anemia	164	58	18	11	9
ID/anemia	261	87	24	13	7

Survival analysis. Kaplan-Meier curves reflecting the difference in event-free survival rates in chronic HF patients with or without ID (A) and between iron-deficient and non-iron-deficient patients with or without anemia (B).